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Solubilization of Hydrophobic Substances into Block Copolymer Micelles in Aqueous Media and Their Release

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13. ABSTRACT (Maximum 200 words)

The objective of this research project was the study of properties of polymer micelles that control the uptake or release of hydrophobic species from aqueous solution. Fluorescence techniques were used to monitor the rate of equilibration of small molecule fluorophores with respect to the micelle interior. An additional goal was to characterize how the properties of the polymer influence the final micelle properties (e.g. aggregation number, hydrodynamic diameter, radius of gyration, etc.). The conditions that permit exchange of individual polymers between micelles have also been determined. Most of our work has involved polymer micelles with polystyrene cores and poly(methylmethacrylate) or poly(t-butylmethacrylate) coronas in organic solvents and poly(methacrylic acid) coronas in aqueous solution.

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**Solubilization of Hydrophobic Substances into Block Copolymer
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Authors: S.E. Webber and P. Munk

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Body of Report

A. Statement of Problem Studied

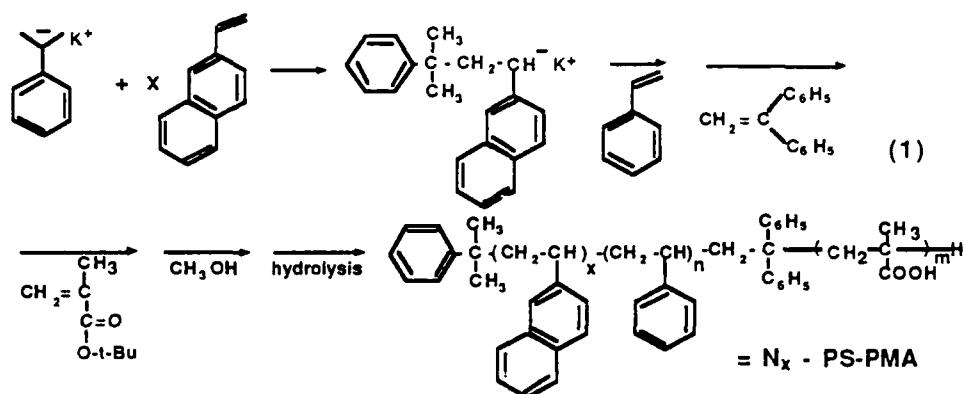
The objective of this research project was originally stated to be the study of properties of polymer micelles that control the uptake or release of hydrophobic species from aqueous solution. As originally conceived fluorescence would be used to monitor the rate of equilibrium of small molecule fluorophores with respect to the micelle interior. As will be discussed in part B, fluorescence techniques were extended beyond this scope. An adjunct goal was to characterize how the properties of the polymer influence the final micelle properties (e.g. aggregation number, hydrodynamic diameter, radius of gyration, etc.). It has been necessary to elucidate how dynamic these micelles are, that is, to determine the conditions that permit exchange of individual polymers. Most of our work has involved polymer micelles with polystyrene cores and poly(methylmethacrylate) or poly(t-butylmethacrylate) coronas in organic solvents and poly(methacrylic acid) coronas in aqueous solution.

B. Summary of Most Important Results

1. Hydrophobic Takeup and Release

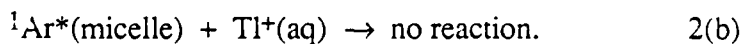
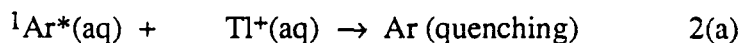
The most convenient kind of hydrophobe for study have been fluorescent species and a great deal of effort has centered on pyrene and more recently, phenanthrene. The former species is a favorite fluorescent probe for a variety of studies including traditional surfactant micelle studies. In our earliest work we found that the takeup of pyrene could be monitored by the change in its fluorescence intensity and spectrum, which is well-known to be environmentally sensitive. We also found that the rate of exchange of small molecules between micelles was very slow (days are required for equilibration) while the capture of these species is very fast. The former has been shown to be the result of very slow diffusion in the glassy core (ca. 10^{-18} cm²/sec) while the latter arises from the very strong partitioning of the hydrophobe into the micelle (the partition coefficient is ca. 1×10^5 for pyrene or anthracene, 6×10^4 for phenanthrene).

We have also synthesized block polymer with small mole fractions of naphthalene groups as fluorescent tags:



These tags can be inserted at the beginning of the sequence (N_x -PS-PMA) or between the PS and PMA blocks (PS- N_x -PMA), which allows us to study processes which primarily affect the micelle core (N_x -PS-PMA) or the core-corona interfacial region (PS- N_x -PMA). These polymers have been invaluable in the present project. For example, naphthalene can be used to sensitize the fluorescence of a hydrophobic probe such as pyrene or anthracene. Therefore sensitized fluorescence can be used to monitor the rate of uptake and release of the probe. Another method based on quenching will be described below. However these tagged polymers can also be used to study the chain mobility by measuring the time dependent fluorescence depolarization. If the core or interfacial region is relatively fluid because of absorption of a swelling solvent, the depolarization is rapid and complete (i.e. there is no residual fluorescence polarization). Thus we have been able to monitor the chain mobility as a function of micelle formation and/or as a function of core swelling. This has been one of the fundamental insights gained from this work that is unique in this field.

In recent work we have used ionic quenchers (Tl^+ , Cu^{+2}) to monitor the takeup and release of fluorescent hydrophobes. The idea is simple. If ${}^1\text{Ar}^*$ is the fluorescent state of the probe, then



Therefore if a micelle saturated with Ar is diluted by addition to a TlNO_3 solution, there will be a steady loss of fluorescence as the probe diffuses out of the micelle and is quenched. The rate of takeup is monitored by adding a small amount of micelle to a saturated aqueous solution of Ar that

contains Tl^+ . In this case the fluorescence grows steadily. These kinetic curves can easily be modeled by classical diffusion equations and analyzed to yield the apparent diffusion constant of the probe in the core.

One disappointing finding is that micelles with glassy cores (PS, PMMA) will solubilize only very hydrophobic species. For example, we have tried to carry out experiments using indomethacin (a common "hydrophobic" drug) and found that it partitions into the micelle relatively poorly. Clearly one must tailor the chemical nature of the core to the absorbate.

2. Fundamental Characterization of the Micelles and Their Dependence on the Constituent Polymer Properties

A great deal of classical background work was carried out on the physical characterization of micelles made from different di-block and tri-block polymers. The techniques applied were: (1) classical light scattering (aggregation number and radius of gyration), (2) quasi-elastic light scattering (hydrodynamic diameter, which is a function of pH), (3) electrophoretic mobility (also a function of pH), (4) sedimentation velocity (demonstrating that a single species was present in most cases, see below), and (5) viscosity. This has led to a body of data that relates the micelle properties to the block length of the constituent polymer. It has also been possible to characterize the kinetic stability of micelles using sedimentation velocity. For micelles with relatively short core-forming blocks polymers can be exchanged between micelles in a mixed organic solvent. Thus if two different micelles are mixed, then under the appropriate conditions polymers are exchanged and an intermediate-sized monodisperse micelle is formed ("micelle hybridization"). However this phenomenon is never observed in aqueous solution where the micelles appear to be totally kinetically inert.

3. Developments Unanticipated in the Original Proposal

(a) Freeze-drying of Micelles

We have found PS-PMA micelles in neutral or basic aqueous solution to be very stable. The solution can be freeze-dried and the powder redispersed into water with essentially the same

hydrodynamic radius as the original solution. This cycle can be repeated 3-4 times before one begins to observe aggregates.

A related procedure was developed for dioxane-water mixtures that are used to prepare the micelles from the polymer. This latter system is a little more difficult because the cores are quite swollen and there is a greater tendency for aggregation. However it has also been found that hydrophobic species can be conveniently loaded into the micelles using this method, although the partitioning into the micelles is less effective because of the higher solubility of the hydrophobic species in the exterior solvent mixture.

It seems likely to us that these procedures could have important technological ramifications. The University of Texas evaluated the potential of these methods for a patent application but the decision was made not to pursue this application at the present time because polymer micelles are not yet used in commercial drug or other chemical delivery systems and it is not clear that there would be a market for this invention.

(b) Surface Modification with Micelles

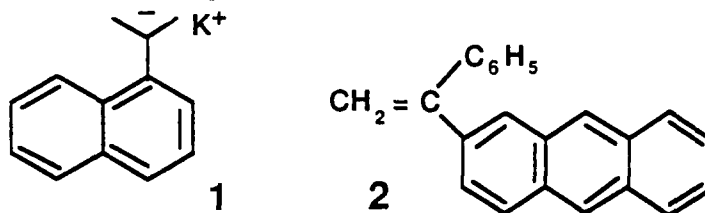
It has been found that under the appropriate conditions that PS-PMA micelles will strongly adsorb onto polystyrene films, decreasing the H₂O contact angle from ca. 90° (pure polystyrene) to ca. 35° (maximum concentration of micelles). SEM images have demonstrated that intact micelles are present on these surfaces. This research effort will be continued with support from other agencies with the primary goal of producing photoactive polymer surfaces.

We have also looked at micelles with end-functionalization (e.g. PS-PtBuMA-NH₂) which can react with modified SiO₂ surfaces. While this treatment also modifies the contact angle of these surfaces, the morphology of the polymers on these surfaces is not yet determined.

(c) Development of New Initiators and Chain Modifiers

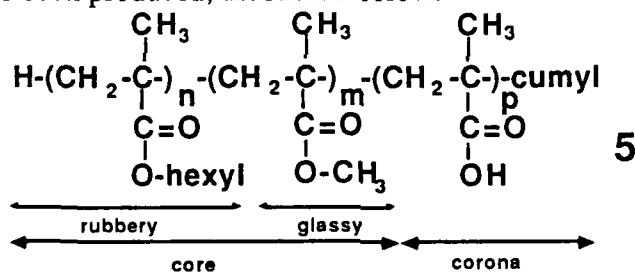
It was indicated earlier that diblock polymers with fluorescence tags are very useful in this research. More precise control of these tags is possible if they are incorporated into either the anionic initiator or a species that can be inserted between the PS and PMA block. Two such

species that have been developed for this work are illustrated below. These have been used to prepare block polymers that can be represented by the formula N-PS-A-PMA.



(d) Development of New Tri-block Polymers

The fact that PS-PMA micelles have a glassy core is manifested by the very small diffusion constants observed (for pyrene, ca. 10^{-18} cm²/sec). Also the ability of glassy cores to solubilize a wide range of absorbates seems to be limited. One can attempt to improve this situations by swelling the core with appropriate solvents, and this is being studied. One can also prepare a tri-block polymer in which the first block is rubbery, with the hope of producing an "onion-skin" structures, with a glassy layer between the inner rubbery region and the corona. A tri-block polymer of this type has been produced, illustrated below:



We have determined that such a polymer does form well-behaved monodisperse micelles in aqueous solution, but very little other characterization has been carried out. We are especially interested in characterizing the take-up and release properties of these micelles.

C. List of Publication

- (1) "Fluorescence Studies of Amphiphilic Poly(methacrylic acid)-*block*-polystyrene-*block*-Poly(methacrylic acid) Micelles", T. Cao, P. Munk, C. Ramireddy, Z. Tuzar, and S.E. Webber, Macromolecules **24**, 6300 (1991).
- (2) "Fluorimetric and QELS Study of the Solubilization of Non-Polar Low-Molar Mass Compounds into Water-Soluble Block-Copolymer Micelles", D. Kiserow, K. Prochazka, C. Ramireddy, Z. Tuzar, P. Munk and S.E. Webber, Macromolecules **25**, 461 (1992).
- (3) "Labeled Polystyrene-*block*-Poly(Methacrylic Acid) Micelles in Aqueous Media", K. Prochazka, D. Kiserow, C. Ramireddy, Z. Tuzar, P. Munk and S.E. Webber, Macromolecules **25**, 454 (1992).
- (4) "Styrene-*t*-Butyl Methacrylate and Styrene-Methacrylic Acid Block Copolymers: Synthesis and Characterization", C. Ramireddy, Zdenek Tuzar, Karel Prochazka, S.E. Webber, and Petr Munk, Macromolecules , **25**, 2541,(1992)
- (5) "Fluorescence Studies of Naphthalene Labeled Diblock and Triblock Copolymer Micelles in Organic Media", D. Kiserow, J. Chan, C. Ramireddy, P. Munk, and S.E. Webber, Macromolecules **25**, 5338 (1992).
- (6) "Block Copolymer Micelles in Aqueous Media" P. Munk, C. Ramireddy, M. Tian, S.E. Webber, K. Procházka, and Z. Tuzar, Makromol. Chem., Macromol. Symp. , **58**, 195 (1992)
- (7) "Study of Sedimentation Velocity of Block Copolymer Micelles" M. Tian, C. Ramireddy, S. Webber, P. Munk Collection of the Czechoslovak Chemical Communication **58**, 71 (1993)
- (8) "Hybridization of Block Copolymer Micelles", M. Tian, A. Qin, Ramireddy, S.E. Webber, P. Munk, Z. Tuzar, K. Procházka, Langmuir **9**, 1741 (1993)
- (9) "Characterization of Block Copolymer Micelles in Aqueous Media", P. Munk, A. Qin, M. Tian, C. Ramireddy, S.E. Webber, Z. Tuzar, and K. Procházka, J. Appl. Polym. Sci., Appl. Polym. Symp., **52**, 45-54 (1993).
- (10) "Fluorescence Studies of Naphthalene Labeled Poly(styrene)-*blk*-poly(methacrylic acid) in Aqueous Solution", J. Chan, D. Kiserow, C. Ramireddy, P. Munk, and S.E. Webber Macromolecules **26**,7016 (1993)

(11) "Polystyrene-Poly(methacrylic acid) Block Copolymer Micelles", A. Qin, M. Tian, C. Ramireddy, S.E. Webber, P. Munk, Z. Tuzar Macromolecules , **27**, 120 (1994)

(12) "Fluorescence Studies of Pyrene Capture by Naphthalene Labeled Diblock Copolymer Micelles in Aqueous Media", S.L. Fox, J. Chan, D. Kiserow, C. Ramireddy, P. Munk, and S.E. Webber (to appear in *Advances in Chemistry*, No. 223, "Water-Soluble and Water-Swellable Polymers", J.E. Glass, Ed.)

(13) "Time-Resolved Fluorescence Anisotropy Measurements on Labelled Polyelectrolyte Micelles", K. Procházka, Z. Limpouchová, S.E. Webber, P. Munk (submitted)

D. Participating Scientific Personnel

Please note that most of the people listed were often supported in part by other grants over the course of this project.

Prof. S.E. Webber and Prof. P. Munk - Co-PIs

Dr. T. Cao, Dr. C. Ramireddy, Dr. A. Qin - postdoctorals

Dr. Z. Tuzar, Dr. K. Procházka - visiting scientists from the Czech Republic

Dr. D. Kiserow - Ph. D. student, degree completed 1992

J. Chan, S. Fox, M. Tian - Ph.D. students, degree to be completed 1994

Inventions: No inventions to report (but see section B, subsection 3(a) of the main report).